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10/509,675	09/13/2006	Piero Del Soldato	026220-00055	3644

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EXAMINER	
LAU, JONATHAN S	

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
08/05/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/509,675	DEL SOLDATO, PIERO	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) *2,5 and 6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4 and 7-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is responsive to Applicant's Amendment and Remarks, filed 28 Apr 2009, in which claims 1 and 9 are amended to change the scope and breadth of the claim.

This application is the national stage entry of PCT/EP03/03183, filed 27 Mar 2003; and claims benefit of foreign priority document ITALY MI2002A00077, filed 11 Apr 2002. An English language translation of the foreign priority document is not currently of record.

Claims 1-9 are pending in the current application. Claims 2, 5 and 6, drawn to a nonelected species, are withdrawn. Claims 1, 3, 4 and 7-9 are examined on the merits herein.

Rejections Withdrawn

Applicant's Amendment, filed 28 Apr 2009, with respect to claims 1, 3, 4 and 7-8 rejected under 35 U.S.C. 102(b) as being anticipated by Armour et al. (Arthritis and Rheumatism, 2001, 44(9), p2185-2192, provided by applicant as reference AN in IDS filed 08 Oct 2004) has been fully considered and is persuasive, as the method of independent claim 1 as amended recites the active step of administering to a subject within a treatment population not explicitly or implicitly disclosed in Armour et al.

because the subject disclosed by Armour et al. is not necessarily in need of treatment for degeneration of the cartilaginoid matrix.

This rejection has been **withdrawn**.

Applicant's Amendment, filed 28 Apr 2009, with respect to claims 1 and 9 rejected under 35 U.S.C. 103(a) as being unpatentable over Armour et al. (Arthritis and Rheumatism, 2001, 44(9), p2185-2192, provided by applicant as reference AN in IDS filed 08 Oct 2004) in view of Gabalawy et al. (Arthritis Res. 2002, 4 (suppl 3), pS297-S301, published 09 May 2002, of record) has been fully considered and is persuasive, as the method of independent claim 1 as amended recites the active step of administering to a subject within a treatment population not explicitly or implicitly taught by Armour et al. in view of Gabalawy et al.

This rejection has been **withdrawn**.

The following new or modified grounds of rejection are necessitated by Applicant's Amendment, filed 28 Apr 2009, in which claims 1 and 9 are amended to change the scope and breadth of the claim. Claims 3, 4 and 7-9 depend from claim 1 and incorporate all limitations therein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Amended Claims 1, 3, 4 and 7-9 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 1 recites "...administering to a subject with arthritis an effective amount of one or more compounds or salts thereof..." Claims 3, 4 and 7-9 depend from claim 1 and incorporate all limitations therein.

The specification discloses chemical salts, such as examples of organic salts: oxalic, tartaric, maleic, succinic, citric, trifluoroacetic acids; and examples of inorganic salts: nitric, hydrochloric, sulphuric, phosphoric acids at page 25, paragraphs 2-3; and the usual excipients of pharmaceutical compositions at page 25, paragraph 5. However, claims 1, 3, 4 and 7-9 are directed to encompass any salts, which only correspond in some undefined way to specifically instantly disclosed chemicals. None of these salts meet the written description provision of 35 USC § 112, first paragraph, due to lacking chemical structural information for what they are and because chemical salts are highly variant and encompass a myriad of possibilities. The specification provides insufficient written description to support the genus encompassed by the claim, and no limiting definition of a "salt" is provided other than the salt of an organic or inorganic acid at page 25, paragraph 1 and non-limiting examples at page 25, paragraphs 2-3.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the

'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of the above specifically disclosed chemical structures, the skilled artisan cannot envision the detailed chemical structure of the encompassed derivatives, analogs, etc., regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The chemical structure itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

Therefore, only the structurally defined chemical compounds, but not the full breadth of the claims, meet the written description provision of 35 USC § 112, first

paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC § 112 is severable from its enablement provision. (See Vas-Cath at page 1115.)

The court of *In re Curtis* held that "a patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when… the evidence indicates ordinary artisans could not predict the operability … of any other species." (see *In re Curtis* 354 F.3d 1347, 69 USPQ2d 1274, Fed. Cir. 2004). The court of *Noelle v. Lederman* also pointed out that generic claim to anti-CD40CR Mabs lacked written description support because there was no description of anti-human or other species Mabs, and no description of human CD40CR antigen. The court further pointed out that attempt to "define an unknown by its binding affinity to another unknown" failed. See 355 F.3d 1343, 69 USPQ2d 1508, Fed. Cir. 2004. Definition of the salt as the product salifiable with an organic or inorganic acid at page 25, paragraph 1 defines the salt by its production using an unknown organic or inorganic acid.

Response to Applicant's Remarks:

Applicant's remarks, filed 28 Apr 2009, have been fully considered and are not persuasive.

Applicant remarks that the context of the claims make clear that the term salts thereof refers to pharmaceutically acceptable salts. However, the context of the claims requires only that the salt can be administered to a subject. The term "pharmaceutically

acceptable salts" is not necessarily inferred by the context of the claims. For example, Perkins (US Patent Application Publication 2002/0041846, published 11 Apr 2002, cited in PTO-892) discloses a radioactive metal complex in the form of a salt that is administered to a subject having its own pharmacological effect (page 1, paragraphs 7-10), encompassed within the genus of a salt that can be administered to a subject. Chen et al. (US Patent Application Publication 2002/0147201, published 10 Oct 2002, cited in PTO-892) discloses active agents made into salts with glycyrrhizin for administration to a subject (abstract). Glycyrrhizin is known to possess anti-viral and hepatoprotective activity. The specification does not reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention as the salt of the radioactive metal complex disclosed by Perkins or as the salt of glycyrrhizin taught by Chen et al. having a distinct pharmacological activity, or the entire genus of salts that can be administered to a subject. As noted above, the specification reasonably conveys to one skilled in the relevant art that the genus of "pharmaceutically acceptable salts" is described, because the understanding within the art is that nature of the biological response to a "pharmaceutically acceptable salt" of a compound is no different to the nature of the response to the parent compound, though the intensity may differ.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended Claims 1, 3, 4 and 7-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Armour et al. (Arthritis and Rheumatism, 2001, 44(9), p2185-2192, provided by applicant as reference AN in IDS filed 08 Oct 2004) in view of Jang et al. (Free Radical Biology & Medicine, 1998, 24(9), p1511-1519, cited in PTO-892).

Armour et al. discloses HTC1026 or flurbiprofen nitroxylbutylester (page 2185, left column, lines 10-11), the elected species, administered in vivo using a mouse model of ovariectomy-induced bone loss (page 2185, left column, lines 16-17). The Merck Index shows the structure of flurbiprofen (The Merck Index, of record). Armour et al. discloses flurbiprofen nitroxylbutylester may be used for treatment of rheumatoid arthritis, characterized by joint inflammation as well as periarticular and systemic bone loss (page 2185, right column, lines 8-12). Armour et al. discloses administration of flurbiprofen nitroxylbutylester by intraperitoneal injections in corn oil (page 2186, right

column, lines 7-9), a method of parenteral administration. Armour et al. discloses HCT1026 retains the anti-inflammatory and analgesic activity of the nonnitrosylated parent compound, flurbiprofen, and that said compound is useful in inflammatory diseases such as rheumatoid arthritis (page 2192, left column, paragraph 1). Armour et al. teaches the administered HTC1026 retains its activity of inhibition of PGE_2 production (page 2187, right column, paragraph 1). Armour et al. teaches it is known in the prior art that there is cross-talk between the nitric oxide (NO) and PGE_2 pathways (page 2185, left column, paragraph 3).

Armour et al. does not specifically teach the method of treating degeneration of the cartilaginoid matrix comprising administering to a subject in need thereof an effective amount of one or more compounds or salts thereof having the formula (I), or the elected species (instant claim 1).

Jang et al. teaches NO is known to play are role in arthritis (abstract) such as rheumatoid arthritis involving the cascade of events leading to loss of articular cartilage and resorption of bone (page 1511, left column, paragraph 1), and teaches in arthritis an increased loss of proteoglycans leads to cartilage dysfunction and eventually irreversible matrix degeneration (page 1515, right column, paragraph 1). Jang et al. teaches both NO from chondrocytes can lead to both matrix degradation and proteoglycan synthesis and matrix synthesis, as well as PGE_2 leading to inflammation and matrix degradation (page 1515, Fig. 1 at top of page). Jang et al. teaches NO may play a chondroprotective role in cartilage matrix metabolism and limit proteoglycan degradation (page 1515, left column, paragraph 2). Jang et al. teaches it was observed

that NO inhibition has elevated PGE_2 levels (page 1516, right column, paragraph 2), and that targeting both PGE_2 and NO by combination therapy may be an attractive intervention (page 1516, right column, paragraph 5).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine Armour et al. in view of Jang et al. Both Armour et al. and Jang et al. are drawn to the treatment of arthritis. One of ordinary skill in the art would be motivated to combine Armour et al. in view of Jang et al. because Jang et al. teaches targeting both PGE_2 and NO by combination therapy may be an attractive intervention and Armour et al. teaches an NSAID that inhibits PGE_2 production containing a NO donor moiety. One of ordinary skill in the art would be motivated to select the patient population of subjects in need of treating degeneration of the cartilaginoid matrix because Jang et al. teaches in arthritis an increased loss of proteoglycans leads to cartilage dysfunction and eventually irreversible matrix degeneration, suggesting treatment of that subpopulation of patients.

Reponse to Applicant's Remarks:

Applicant's Remarks, filed 28 Apr 2009, have been fully considered and not found to be persuasive.

Applicant provides evidence that the role of NSAIDs on cartilage in arthritic patients is unpredictable. This evidence is not persuasive in view of the teaching of Armour et al. in view of Jang et al. that both there is cross-talk between the nitric oxide (NO) and PGE_2 pathways and that both pathways play a role in cartilage matrix degradation.

Jang et al., published in 1998, suggests that the role of NO in arthritic patients is also ambiguous, concluding that further investigation is required whether NO-mediated effects in cartilage lead to or accelerate the pathogenesis of arthritis but, despite mounting evidence for NO in catabolic events, data also exist to suggest that NO is protective at least for the cartilage matrix (page 1517, left column, section Concluding Remarks). However, in view of the understanding of the metabolic pathways at the time of the invention as illustrated in Jang et al. at page 1515, figure 1, and the express suggestion of Jang et al. for targeting both PGE_2 and NO by combination therapy, it would have been *prima facie* obvious with a reasonable expectation of success to combine Armour et al. in view of Jang et al.

It is noted that the data provided in the specification compare NO-flurbiprofen with flurbiprofen at pages 40, 42, 43 and 44. No comparison is made to the effect of NO itself. Jang et al. teaches that NO also plays a role in cartilage matrix metabolism and teaches that data suggest it is protective for the cartilage matrix and Armour et al. teaching a compound containing moieties that target both PGE_2 and NO.

Amended Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Armour et al. (Arthritis and Rheumatism, 2001, 44(9), p2185-2192, provided by applicant as reference AN in IDS filed 08 Oct 2004) in view of Jang et al. (Free Radical Biology & Medicine, 1998, 24(9), p1511-1519, cited in PTO-892) as applied to claims 1, 3, 4 and 7-8 above, and further in view of Gabalawy et al. (Arthritis Res. 2002, 4 (suppl 3), pS297-S301, published 09 May 2002, of record).

Armour et al. in view of Jang et al. teaches as above.

Armour et al. in view of Jang et al. does not specifically disclose the method wherein relapses of degeneration of the cartilaginoid matrix are reduced.

Gabalawy et al. teaches relapse of rheumatoid arthritis is almost predictable after withdrawal of the antirheumatic drugs currently used in clinical practice (page S299, left column, paragraph 3). Gabalawy et al. teaches sustained or ongoing therapy may be used to reduce the possibility of a relapse (page S300, left column, paragraph 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine Armour et al. in view of Jang et al. and further in view of Gabalawy et al. Both Armour et al. and of Gabalawy et al. are drawn to drugs to treat rheumatoid arthritis. One of ordinary skill would have been motivated to combine Armour et al. in view of Jang et al. and further in view of Gabalawy et al. because Gabalawy et al. teaches antirheumatic drugs currently used in clinical practice can be applied in sustained or ongoing therapy to reduce the possibility of a relapse.

Reponse to Applicant's Remarks:

Applicant's Remarks, filed 28 Apr 2009, have been fully considered and not found to be persuasive.

Applicant's remarks regarding Armour et al. are addressed as above.

Conclusion

No claim is found to be allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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